



Is aberrant affective cognition an endophenotype for affective disorders? - A monozygotic twin study

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36 **Abstract**

37 **Background:** Identification of endophenotypes can improve prevention, detection and development
38 of new treatments. We therefore investigated whether aberrant affective cognition constitutes an
39 endophenotype for affective disorders by being present in monozygotic (MZ) twins with unipolar or
40 bipolar disorder in partial remission (i.e. affected) and their unaffected co-twins (i.e. high-risk)
41 relative to twins with no family history of affective disorder (i.e. low-risk).

42

43 **Methods:** We conducted an assessor blind cross-sectional study from 2014–2017 of MZ twins
44 using Danish population-based registers in recruitment. Twins attended one test session involving
45 neurocognitive testing, clinical ratings and questionnaires. Main outcomes were attention to and
46 recognition of emotional facial expressions, memory of emotional self-referential words, emotion
47 regulation and coping strategies.

48

49 **Results:** Participants were 103 affected, 44 high-risk and 36 low-risk MZ twins. Groups were
50 demographically well-balanced and showed comparable non-affective cognitive performance. We
51 observed no aberrant affective cognition in affected and high-risk relative to low-risk twins.
52 However, high-risk twins displayed attentional avoidance of emotional faces ($P_s \leq .009$) and more
53 use of task-oriented coping strategies ($P = .01$) compared with affected twins. In contrast affected
54 twins showed more emotion-oriented coping than high- and low-risk twins ($P_s \leq .004$).

55

56 **Conclusions:** Our findings provide no support of aberrant affective cognition as an endophenotype
57 for affective disorders. High-risk twins' attentional avoidance of emotional faces and greater use of
58 task-oriented coping strategies may reflect compensatory mechanisms.

59

60 **Introduction**

61 Endophenotypes are trait-related illness biomarkers observable in individuals at familial risk that
62 have attracted great research attention as they may aid prevention, early detection and development
63 of targeted treatments (Gottesman & Gould 2003). Aberrant affective cognition is a putative
64 endophenotype for affective disorders involving attention to, encoding and memory of stimuli with
65 affective salience, as well as the regulation of the emotional response to such stimuli (Elliott *et al.*
66 2011). In particular, current neurocognitive models of affective disorders put negative bias in
67 affective cognition at the core of illness development (Phillips *et al.* 2008; Roiser 2013; Malhi *et al.*
68 2015).

69 Considerable research on euthymic patients with unipolar disorder (UD) and bipolar disorder
70 (BD) point to aberrant affective cognition as a trait marker (Leppänen 2006; Rocca *et al.* 2009;
71 Mercer & Becerra 2013; Miskowiak & Carvalho 2014). Replicated findings are negative emotional
72 bias and general deficits in the recognition of emotional faces (Leppänen 2006; Rocca *et al.* 2009;
73 Mercer & Becerra 2013; Miskowiak & Carvalho 2014), although bias in attention and memory is
74 also observed (Leppänen 2006; Rocca *et al.* 2009; Mercer & Becerra 2013; Miskowiak & Carvalho
75 2014). Two recent studies have demonstrated reduced emotion regulation ability in remitted BD
76 patients (Rive 2015; Kjørstad *et al.* 2016).

77 Studies of **adult** individuals at familial risk provide emerging evidence of aberrant affective
78 cognition as risk markers of affective disorder (Miskowiak & Carvalho 2014; Miskowiak *et al.*
79 2017). **However, abnormalities seem to especially characterize individuals at risk of UD (Le**
80 **Masurier *et al.* 2007; Miskowiak *et al.* 2015) rather than individuals at risk of BD (de Brito Ferreira**
81 **Fernandes *et al.* 2016; McCormack *et al.* 2016).** Maladaptive coping strategies (e.g. emotion-
82 oriented) have been observed in high-risk individuals (Vinberg *et al.* 2010; Green *et al.* 2011).
83 Nevertheless, findings are inconsistent and there is a paucity of studies of genetically well-defined

adult risk samples. Additional methodological issues include differences in paradigms and analyses, a shortage of studies investigating performance across domains and — especially for the UD literature — studies where high-risk individuals are compared directly with affected probands.

Assessment of monozygotic (MZ) twins represents a strong methodology for endophenotype research because MZ twins share 100% of their segregating genes and early environment (Boomsma *et al.* 2002). In discordant twin pairs the unaffected twin is at ultra-high risk because of being genetically identical to the affected twin. This is reflected by the high concordance rates of 23–67% in UD and 44–62% in BD MZ twin pairs (McGuffin *et al.* 1996; Sullivan *et al.* 2000). Only one previous MZ twin study has investigated association of aberrant affective cognition with familial risk defined as having a co-twin with a history of depression. This study revealed negative bias in attentional to and deficits in the recognition of facial expressions MZ high-risk twins (Miskowiak *et al.* 2015).

The aim of the present study was to investigate if aberrant affective cognition constitutes an endophenotype for affective disorder by comparing several key domains of affective cognition between: (1) affected MZ twins in partial remission; (2) unaffected high-risk MZ twins with a co-twin history of affective disorder; (3) and low-risk MZ twins with no personal or first-degree history of affective disorder. We hypothesized that both affected twins and — to a lesser degree — high-risk twins would have general deficits in the recognition of emotional faces, negative bias in face processing (i.e. reduced attention to and/or recognition of happy vs. fearful faces) and/or in self-referential memory, reduced ability to down-regulate emotions in social scenarios and maladaptive habitual coping compared with low-risk twins.

Methods

Participants and recruitment

108 A nationwide record linkage of the Danish Twin Registry (Skytthe *et al.* 2013), the Danish
109 Psychiatric Central Research Register (Mors *et al.* 2011) and the Danish Civil Registration System
110 (Pedersen 2011) identified eligible twins by the following criteria: (1) monozygosity; (2)
111 concordance or discordance of UD or BD from January 1995 to June 2014; (3) age 18–50 years (at
112 the register linkage date 1th June 2014). Exclusion criteria were birth weight < 1.3 kg, current severe
113 somatic illness, history of brain injury, current substance abuse, current mood episode (i.e.
114 Hamilton Depression Rating Scale (HDRS-17) or Young Mania Rating Scale (YMRS) > 14),
115 pregnancy and dizygosity. Unaffected twin pairs were excluded if having first-degree relatives with
116 organic mental disorder, schizophrenia spectrum disorders or affective disorders. Zygoty was
117 estimated with the twin likeness questionnaire from the Danish Twin Registry. However, pair-wise
118 DNA tests were conducted if zygoty was considered uncertain.

119 ***Procedure***

120 This study is part of a nationwide cross-sectional assessor-blind study of putative epigenetic,
121 cellular, neurocognitive and imaging endophenotypes for affective disorders in MZ twins.
122 Participants were invited to a single day assessment from 8.30 a.m. to 3–7 p.m. After informed
123 consent the following assessments were conducted chronologically: mood ratings using the HDRS-
124 17 (Hamilton 1967) and YMRS (Young *et al.* 1978), biological material sampling, a semi-
125 structured diagnostic interview using the Schedules for Clinical Assessment in Neuropsychiatry
126 (SCAN) (Wing *et al.* 1990), two hours of neurocognitive testing and — for a subgroup — functional
127 magnetic resonance imaging. All assessors were blinded for the diagnostic status of participants
128 during data collection.

129 ***Questionnaires***

130 Participants completed the following questionnaires: The Major Depression Inventory (MDI) (Bech
131 *et al.* 2001), The State-Trait Anxiety Inventory form Y (STAI-Y)(Spielberger 1989), the Eysenck
132 Personality Questionnaire (EPQ) (Eysenck 1975) and The Coping Inventory of Stressful Situations
133 (CISS) (Endler & Parker 1990).

134 *Assessment of non-affective cognition*

135 Premorbid verbal intelligence was estimated with the Danish Adult Reading Task (DART) (Nelson
136 & O'Connell 1978). Brief assessment of non-affective cognitive performance was conducted using
137 the Screen of Cognitive Impairment in Psychiatry (SCIP-D) (Purdon 2005) and The Trail Making
138 Test parts A and B (TMT A/B) (Army Individual Test Battery, 1944).

139 *Assessment of affective cognition*

140 Emotional processing was investigated with the following computerized tests from the Emotional
141 Test Battery (PIVital; Oxford Emotional Test Battery [ETB] 2017): The Faces Dot-Probe Task, the
142 Facial Expression Recognition Task and the Emotional Categorisation and Recall Tasks. Emotion
143 reactivity and regulation were assessed with the Social Scenarios Task (Goldin *et al.* 2009;
144 Kjærstad *et al.* 2016).

145 In the Faces Dot-Probe Task, pairs of happy-neutral, fearful-neutral or neutral-neutral faces
146 were presented horizontally unmasked (100 ms) or masked (17 ms). One of the faces was
147 immediately replaced by two dots presented either vertically (:) or horizontally (· ·). Participants
148 were instructed to indicate the orientation of the dots as quickly and accurately as possible by
149 pressing labelled keys on the keyboard. The task consisted of 32 trials of six conditions: masked or
150 unmasked happy-neutral pairs, fearful-neutral pairs and neutral-neutral pairs. Eight blocks of

151 unmasked and eight blocks of masked trials were presented in an alternating order, where each
152 block consisted of 12 trials including all three types of face pairs (Murphy *et al.* 2008).

153 For the Facial Expression Recognition Task, pictures of faces taken from Ekman & Friesen
154 (1979) expressing one of six basic emotions: anger, disgust, fear, happy, sad and surprised were
155 displayed morphed at 10% intensity levels between a neutral face (0%) and a full emotional face
156 (100%). Participants were instructed to determine the emotional expression as quickly and
157 accurately as possible by pressing the corresponding key on the keyboard. Participants viewed 250
158 faces presented in randomized order for 500 ms, immediately replaced by a black screen. The faces
159 consisted of four examples of every emotion at each intensity level plus a neutral face for every
160 emotion (Harmer *et al.* 2004).

161 The Emotional Categorisation and Recall Tasks involved presentation of 45 positive and 45
162 negative personality characteristics taken from Anderson's list of personality-trait words (Anderson
163 1968). Words were matched on length and ratings of frequency and meaningfulness, translated to
164 Danish and displayed for 500 ms in a randomized order, separated by a fixation cross displayed for
165 500 ms. Participants were instructed to categorise personality trait words as referring to likeable or
166 dislikeable attributes as quickly and accurately as possible. This categorization was performed in a
167 self-referential manner where participants imagined overhearing someone talking about them, using
168 these words about them. A recall task was given fifteen minutes after completion, where
169 participants were asked to state words remembered from the categorisation task within five minutes.

170 Finally, the Social Scenarios Task involved presentation of highly positive and negative social
171 scenarios by short written paragraphs followed by associated self-beliefs statements (e.g. you are
172 outstanding, you don't fit in). Each scenario consisted of 11 sentences describing the situation (3s
173 each), 10 self-beliefs (3s each) and 10 corresponding emotion ratings. Participants were instructed
174 to either react naturally or dampen their emotional responses by cognitive reappraisal and to judge

175 their emotional state on a scale from 1 to 100 representing degree of discomfort/sadness or
176 pleasure/happiness. The first scenario was neutral followed by two scenarios of same valence with
177 alternate react/dampen conditions. After assessing sexual orientation, participants were given one of
178 two versions involving attraction to/rejection by a man or a woman.

179 ***Equipment***

180 The Facial Expression Recognition and Emotional Categorisation Tasks were administered on a
181 Dell PP18l laptop computer using Superlab Pro version 1.05. The Faces Dot-Probe and Social
182 Scenarios Tasks were administered on a Lenovo T450s laptop computer using E-Prime Version 2.0.

183 ***Data analysis***

184 In the *primary analysis*, the three risk groups were compared on the following variables of interest:
185 (1) attentional vigilance to fear and happiness, (2) discrimination of facial expressions in general
186 and of happiness and fear, specifically, (3) emotional reactivity and down-regulation to positive and
187 negative scenarios; (4) categorisation and recall of positive and negative self-referential words, and
188 (5) self-reported habitual coping strategies. In the *secondary explorative analyses*, we compared (1)
189 complete twin pairs grouped according to pairwise history of affective disorders as concordant,
190 discordant and unaffected twin pairs and (2) affected and unaffected twins from discordant twin
191 pairs. The two-high-threshold model was applied to obtain a measure of discrimination accuracy of
192 facial expressions (d') by the formula: $([\text{number of hits}+0.5]/[\text{number of targets}+1]) - ([\text{number of}$
193 $\text{false alarms}+0.5]/[\text{number of distractors}+1])$ (Corwin 1994) and response bias by the formula:
194 $([\text{number of false alarms}+0.5]/[\text{number of distractors}+1]) / [1 - \text{discrimination accuracy}]$ (Chronaki *et*
195 *al.* 2015). Vigilance scores were calculated as response time latency identifying probes after neutral
196 faces versus emotional faces.

197 Data analyses were conducted in SAS 9.4 (SAS Institute Inc.). Continuous variables were
198 examined with mixed model analysis of variance with random effects for twin pairs to account for
199 dependence within these. In analysis of the ten intensity levels of happy and fearful faces, we used
200 logistic regression techniques with nested random effects for twin and subject to jointly consider the
201 different levels. Categorical variables were also compared using logistic regression, where within
202 twin-pair dependence was adjusted for using GEE estimates of the standard errors. Group
203 comparisons were considered as fixed factors. Affected and unaffected co-twins of discordant twin
204 pairs were compared using parametric paired samples t-tests, with the exception of non-parametric
205 tests for intensity levels of facial expressions. Experimental paradigms involving repeated
206 measurements (i.e. emotional expression of faces, positive and negative words and react and
207 dampen conditions) were modelled using nested random effects for twin pairs and subjects. All
208 primary analyses were performed unadjusted and adjusted for HDRS-17 scores (i.e. depressive
209 symptoms). Two sensitivity analyses were conducted. Firstly, we tested the influence of BD by
210 excluding participants with or at risk of BD from analyses. Secondly, we tested the influence of
211 antidepressants by excluding participant with current antidepressant usage from analyses. The
212 significance level was set to $\alpha=.05$ and hypotheses tests were two-sided. Analyses were not
213 corrected for multiple comparisons given the explorative nature of the study.

214

215 **Results**

216 *Participants*

217 Of 476 eligible MZ twins identified by the register linkage, we invited 408 twins to take part in the
218 study between December 2014 and January 2017. Of these, 44 were excluded: (1) two were dead;
219 (2) four were dizygotic; (3) ten had birth weight < 1300g; (4) three had a history of severe head

220 trauma; (5) three had severe somatic illness (chronic myelogenous leukaemia, severe anorexia
221 nervosa, multiple sclerosis); (6) three had current alcohol abuse; (7) five had a current mood
222 episode; (8) three were pregnant; (9) two had Asperger syndrome. Additionally, nine low-risk twins
223 were excluded due to having a first-degree relative with a psychiatric disorder. Of the remaining
224 364 eligible participants, 209 (affected: $n = 119$, high-risk: $n = 50$, low-risk: $n = 40$) agreed to
225 participate (inclusion rate 57%). We excluded one high-risk twin and four affected twins from the
226 analysis after interviews because of being diagnosed with, or being at risk of, schizophrenia
227 spectrum disorders. Due to a technical issue with the test computer, affective cognition data were
228 lost for 21 participants (affected: $n = 12$, high-risk: $n = 5$, low-risk: $n = 4$). The finale sample of 183
229 MZ twins (affected: $n = 103$, high-risk: $n = 44$, low-risk: $n = 36$) consisted of 79 complete twin
230 pairs and 25 twin individuals whose co-twin was not included in the analyses. Of the 79 complete
231 twin pairs, 22 were concordant, 40 were discordant and 17 were unaffected twin pairs. Among the
232 44 high-risk twins, 34 (77%) had a co-twin diagnosed with UD and 10 (23%) with BD.

233 Affected, high-risk and low-risk groups were well-balanced with respect to age, sex, years of
234 education and premorbid IQ ($P_s \geq .16$, Table 1). However, affected twins exhibited more depression
235 and anxiety symptoms and scored higher on neuroticism than high- and low-risk twins ($P_s < .001$,
236 Table 1). Importantly, there were no group differences in non-affective cognitive performance ($P_s \geq$
237 .15, Table 2).

238 *Attention to and recognition of emotional faces*

239 Comparing vigilance scores with zero across all participants revealed subliminal attentional
240 avoidance of happy faces ($t = -4.16$, $df = 180$, $P < .001$) and a tendency of supraliminal attentional
241 avoidance of happy faces ($t = -1.92$, $df = 180$, $P = .056$), but no attentional bias or avoidance of
242 fearful faces ($P_s \geq .70$). We found group differences in subliminal vigilance to happy faces ($F = 4.7$,

243 $df = 2, 177, P = .01$) and supraliminal vigilance to fearful faces ($F = 3.6, df = 2, 177, P = .03$), in
244 the absence of differences in subliminal vigilance to fearful faces or supraliminal vigilance to happy
245 faces ($Ps \geq .60$, Table 3 and Figure 1). These group differences were driven by subliminal
246 attentional avoidance of happy faces ($P = .003$) and supraliminal attentional avoidance of fearful
247 faces ($P = .009$) in high-risk versus affected twins. Differences prevailed after adjusting for
248 depressive symptoms ($Ps \leq .02$).

249 Participants generally displayed a positive bias in recognition of facial expressions as reflected
250 by increased discrimination accuracy ($F = 205.7, df = 1, 181, P \leq .001$) and shorter response times
251 ($F = 339.4, df = 1, 180, P \leq .001$) to happy than fearful faces, although participants were more
252 likely to categorise faces as fearful than happy ($F = 67.0, df = 181, P \leq .001$). There were no group
253 differences in discrimination accuracy, speed during recognition or response bias of fear and happy
254 or other emotional expressions ($Ps \geq .19$, Table 3). Analysis of the ten intensity levels of fearful and
255 happy faces revealed no group by task interactions ($Ps \geq .99$).

256 *Self-referential categorisation and memory*

257 Participants generally displayed a positive bias in categorisation of self-referential personality trait
258 words as reflected by shorter response times to positive than negative words ($F = 53.8, df = 1, 163,$
259 $P < .001$), but there were no differences in categorisation accuracy or recall of positive versus
260 negative words ($Ps \geq .17$). We found no group differences in speed or accuracy during
261 categorisation or recall of positive and negative self-referential personality trait words, with or
262 without adjustment for depressive symptoms ($Ps \geq .08$, Table 3).

263 *Emotional reactivity and regulation to social scenarios*

264 In the ‘react’ conditions, negative and positive social scenarios elicited more unpleasant and
265 pleasant emotional responses, respectively, compared with the neutral scenario (negative: $F =$
266 1273.7 , $df = 1, 169$, $P < .001$; positive: $F = 1533.6$, $df = 1, 168$, $P < .001$). In the ‘dampen’
267 conditions, participants were generally able to dampen their negative and positive emotional
268 responses (negative: $F = 281.4$, $df = 1, 169$, $P < .001$; positive: $F = 207.4$, $df = 1, 167$, $P < .001$).
269 We found no significant group differences in emotional reactivity to negative ($P = .08$) or positive
270 ($P = .33$) social scenarios. However, explorative pairwise comparisons suggested that affected twins
271 experienced more unpleasant emotions than low-risk twins when instructed to ‘react’ in negative
272 scenarios ($t = 1.99$, $df = 169$, $P = .049$). We found no group differences in the ability to down-
273 regulate emotional reactions to negative or positive scenarios, with or without adjustment for
274 depressive symptoms (P s $< .26$, Table 3).

275 *Habitual coping strategies*

276 We found group differences in the use of emotion-oriented ($F = 7.8$, $df = 2, 159$, $P < .001$) and task-
277 oriented ($F = 3.2$ $df = 2, 159$, $P = .04$) coping (Table 3). These differences were driven by increased
278 use of task-oriented coping in high-risk twins relative to affected twins ($P = .01$) and by more use of
279 emotion-oriented coping in affected twins relative to both high-risk ($P = .004$) and low-risk ($P =$
280 $.001$) twins. The greater use of emotion-oriented coping strategies in affected twins prevailed after
281 adjustment for depressive symptoms ($P = .03$).

282 *Sensitivity analysis*

283 Omitting the BD subgroup rendered non-significant group differences in supraliminal vigilance to
284 fearful faces ($P = .06$) and task-oriented coping ($P = .14$). Omitting participants on antidepressants
285 rendered non-significant group differences in task-oriented coping ($P = .31$). All other outcomes
286 remained statistically significant.

287 *Secondary analysis*

288 Comparable to the primary analysis, unaffected co-twins in discordant twin pairs showed
289 supraliminal attentional avoidance of fearful faces ($P = .002$), and more use of task-oriented coping
290 ($P = .02$) compared with the affected twins. Concordant twin pairs and affected twins from
291 discordant twin pairs reported more use of emotion-oriented coping than low-risk twin pairs ($P =$
292 $.006$) and unaffected co-twins ($P = .001$), respectively. Specifically for complete twin pair analyses,
293 we found a group difference in speed when categorising self-referential personality trait words ($F =$
294 3.3 , $df = 2, 143$, $P = .04$). This difference was driven by slower responses in concordant twin pairs
295 than unaffected twin pairs ($P = .01$). No other secondary analyses yielded group or group by task
296 interaction effects.

297

298 **Discussion**

299 We investigated whether aberrant affective cognition is an endophenotype for affective disorder by
300 comparing monozygotic affected ($n = 103$), high-risk ($n = 44$) and low-risk ($n = 36$) twins. In
301 contrast with our hypotheses, there were no abnormalities in affective cognition across affected and
302 high-risk relative to low-risk twins. High-risk twins displayed attentional avoidance of emotional
303 faces and more habitual use of task-oriented coping relative to affected twins but did not differ on
304 these measures from low-risk twins. Affected twins showed more use of emotion-oriented coping
305 than both high-risk and low-risk twins.

306 The absence of negative bias and deficits in facial expression recognition contrasts with
307 increased attentional vigilance to fearful faces and face recognition difficulties in MZ twins at risk
308 of UD (Miskowiak *et al.* 2015). In particular, discrepancies may be due to our high-risk sample
309 being younger (mean age 37 vs. 47). However, risk of onset may not decline with age (Vinberg *et*
310 *al.* 2013), suggesting that these samples are at comparable risks. Another difference was the

311 exclusion of twins with any axis-1 diagnosis in the previous study. However, allowing for minor
312 psychiatric disorders would be expected to be associated with more (rather than less) emotion
313 processing abnormalities. Moreover, the previous study included twins at risk of UD only,
314 compared with twins at risk of UD constituting 77% of all at-risk twins in the present study. Since
315 our sensitivity analyses of twins at risk of UD rendered attentional avoidance of subliminally
316 processed happy faces as significant, effect of diagnosis does not explain differences. Finally, the
317 two studies differ in statistical procedure as the present study accounted for covariance within twin
318 pairs. This was not necessary in the previous study because of including only one twin per twin pair.
319 Other findings point to a specific change in fear recognition in individuals at risk for UD with
320 observations of both faster (Le Masurier *et al.* 2007) and slower (Watters *et al.* 2013) reaction time
321 to fearful faces. One could argue that both findings reflect a negative bias with faster reaction time
322 reflecting increased recognition, whereas slower reaction time could reflect more engagement in
323 fearful expressions. However, in line with the present study, the slower reaction time to fearful faces
324 in the large study by Watters and colleagues (high-risk: $n = 101$) could also be interpreted as
325 absence of bias. Moreover, our results corroborate with three large studies that detected no deficits
326 in face recognition in adult samples at risk of UD (Mannie *et al.* 2007) and BD (de Brito Ferreira
327 Fernandes *et al.* 2016; McCormack *et al.* 2016). Overall, the finding of a negative bias in emotional
328 face processing is exclusively reported in small studies (high risk: $n = 13-25$), while absence of
329 deficits and negative bias are reported in larger studies (high-risk: $n = 26-101$). This raises concerns
330 of spurious findings in the small studies and a publication bias (Porter *et al.* 2017). In light of the
331 present negative finding and the paucity of studies of adult first-degree relatives due to a
332 predominant use of child and adolescent samples (e.g. Hanford *et al.* 2016; Sharma *et al.* 2016),
333 there is no strong support for abnormalities in processing of emotional faces as an endophenotype.

334 The absence of negative bias in the recall of self-referential words in high-risk twins is in line
335 with previous findings in individuals at risk of UD (Le Masurier *et al.* 2007; Mannie *et al.* 2007)
336 and in twins at high-risk of UD (Miskowiak, *et al.* unpublished observations). However, while we
337 found no deficits in the categorisation of emotional words, previous UD high-risk studies reported
338 slower response times in general (Mannie *et al.* 2007) and faster categorisation of negative words
339 (Le Masurier *et al.* 2007). Discrepancies may be due to small sample size (high risk: $n = 21$) (Le
340 Masurier *et al.* 2007) and investigation of individuals at-risk of UD only. From these few studies
341 conducted, there is no evidence suggesting that negative bias in emotional recall is an
342 endophenotype. Rather, negative memory bias seems to represent a scarring effect that to some
343 degree is present in remitted patients (Mercer & Becerra 2013; Miskowiak & Carvalho 2014).

344 Our demonstration of no emotion regulation difficulties contrasts with one report of less
345 success in down-regulating positive emotions through reappraisal in first-degree relatives of BD
346 probands (Kanske *et al.* 2015). Discrepancies may be due to diagnosis specific effects and a small
347 sample (high-risk: $n = 17$). However, this aspect of cognition is critically understudied as no other
348 study has been conducted of individuals at familial high-risk. There is a need for future research on
349 emotion regulation to clarify whether this constitutes an endophenotype for affective disorders.

350 The more frequent use of task-oriented coping in high-risk twins compared with affected twins,
351 is in keeping with one previous study demonstrating greater use of adaptive coping strategies (i.e.
352 putting in perspective) in first-degree relatives compared with their BD probands (Green *et al.*
353 2011). However, familial risk of affective disorder has also been associated with increased use of
354 maladaptive coping strategies (e.g. self-blame) compared with affected BD probands (Green *et al.*
355 2011) and individuals at low risk for affective disorder (Vinberg *et al.* 2010; Green *et al.* 2011).
356 Discrepancies may relate to use of different assessment tools: the Coping Inventory in Stressful
357 Situations (Vinberg *et al.* 2010) and the Cognitive Emotion Regulation Questionnaire (Green *et al.*

2011). Although this preliminary evidence point to both adaptive and maladaptive coping being present in high-risk samples, there is a paucity of studies of this clinically relevant topic.

Attentional avoidance of emotional faces and greater use of task-oriented coping in high-risk twins may reflect compensatory strategies. Specifically, the genetic and environmental vulnerability of having a MZ co-twin with affective disorder may promote the development of cognitive strategies that protect against illness onset. Markers specific to high-risk individuals that are not observed in affected or low-risk groups may be interpreted as markers of resilience (Frangou 2011). Notably, recent functional imaging studies showed that resilience to BD was associated with increased integration of the default mode network (Doucet *et al.* 2017) and hyperconnectivity of the ventral visual stream during face processing (Dima *et al.* 2016). Moreover, direct comparison of affected and unaffected twins in discordant pairs revealed similar findings compared to the primary analyses, pointing to differences being due to environmental factors as the MZ twin pairs have almost identical genes.

Replication of the findings of increased use of emotion-oriented coping (e.g. get angry, become tense) in affected individuals across analyses makes this a robust marker associated with history of mood episodes, in line with previous findings (Christensen & Kessing 2005).

It is a limitation that we did not include dizygotic twins since this enables investigation of the interaction between environmental and genetic influence on variance, preferable when investigating endophenotypes. Our population-based sampling strategy using public registers to identify eligible participants reduces selection bias, but does not account for cases in which treatment is not sought. Foremost, we could have increased power in statistical inference by inclusion of more high- and low-risk twins. However, as especially BD has a high heritability, the number of available discordant MZ twin pairs was limited ($n = 63$). Our sample is relatively small compared with other recent studies of individuals at familial risk (high-risk: $n \approx 100$) (Watters *et al.* 2013; McCormack *et*

382 *al.* 2016), but large compared with studies using MZ twins as high-risk participants (Gourovitch *et*
383 *al.* 1999; Hsu *et al.* 2014; Miskowiak *et al.* 2015). Participants taking psychotropic medication were
384 not excluded, although antidepressants have shown to normalize disruptions in affective cognition
385 (Harmer *et al.* 2011). To account for this, we conducted sensitivity analyses excluding participants
386 taking antidepressants. Finally, collapsing the two discrete diagnoses BD and UD hinders
387 classification of diagnosis specific endophenotypes needed to increase diagnostic precision.
388 Nonetheless, we examined risk of affective disorders as deficits in emotion processing have been
389 found across distinct categorical disorders (e.g. BD, UD and anxiety disorders) (Kret & Ploeger
390 2015) and because UD and BD share genetic underpinnings (Cross-Disorder Group of the
391 Psychiatric Genomics Consortium 2013).

392 In conclusion, our findings provide no support for aberrant affective cognition as an
393 endophenotype for affective disorders. Rather, high-risk twins' attentional avoidance of emotional
394 faces and greater use of task-oriented coping might reflect compensatory strategies that help them
395 withstand disease onset despite their biological vulnerability. Implications for future research are
396 increased focus on longitudinal comparisons of genetically well-defined risk samples with both
397 affected and controls, using tools probing cognitive aspects of both resilience and risk.

398

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402

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Conflict of interest

CJH has received consultancy fees from P1vital ltd, Lundbeck, Servier, and Eli-Lilly and is a company director of Oxford Psychologists ltd. CJH has also received grant income from GSK, UCB, Janssen Inc, Lundbeck, Servier and Astra Zeneca. LVK reports having been a consultant for Lundbeck, AstraZeneca and Sunovion within the last 3 years. MV has received consultant fee from Lundbeck and AstraZeneca within the last three years. KWM reports having received consultancy fees from Lundbeck and Allergan in the past 3 years.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of local ethics committee (H-3-2014-003) and data protection agency (2014-331-0751) and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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554

Table 1. Demographic and clinical characteristics of affected, high-risk and low-risk MZ twins

Affected twins	High-risk twins	Low-risk twins	<i>P</i>	Pairwise
(n = 103)	(n = 44)	(n = 36)		comparisons

Age, mean (range), years	36.1 (18.7-52.1)	36.7 (18.7-51.9)	36.2 (19.2-51.7)	.90	
Sex, % (ratio), women	74 (76/103)	73 (32/44)	78 (23/36)	.87	
Education, mean (CI), years	14.4 (13.8-15.0)	15.4 (14.5-16.4)	14.8 (13.1-16.5)	.17	
Premorbid IQ*, mean (CI)	112.9 (111.6-114.2)	12 (109.9-114.0)	109.2 (105.1-113.3)	.16	
Unipolar disorder, % (ratio)	74 (76/103)	NA	NA		
Bipolar-I disorder, % (ratio)	18 (19/103)	NA	NA		
Bipolar-II disorder, % (ratio)	8 (8/103)	NA	NA		
Age at onset, mean (CI), years	23 (22-24)	NA	NA		
Number of episodes, mean (CI)	3 (3-4)	NA	NA		
Anxiety disorders, % (ratio)	7 (7/103)	11 (5/44)	3 (1/36)		
Prior substance abuse, % (ratio)	2 (2/103)	0	0		
Other diagnoses†, % (ratio)	5 (5/103)	0	0		
Medication, % (ratio), yes	55 (57/103)	7 (3/44)	0		
SSRI, SNRI or TCA	40 (41/103)	2 (1/44)	0		
Antipsychotic drugs	15 (15/103)	0	0		
Mood stabilizers‡	17 (18/103)	0	0		
HDRS-17, mean (CI)	4.7 (4.1-5.3)	2.8 (1.9-3.7)	1.8 (0.8-2.8)	<.001	AF>HR&LR
YMRS, mean (CI)	1.8 (1.4-2.2)	1.5 (0.9-2.1)	1.2 (0.6-1.8)	.19	
MDI, mean (CI)	9.1 (7.8-10.6)	5.5 (4.3-6.9)	4.8 (3.7-6.3)	<.001	AF>HR&LR
STAI-State, mean (CI)	31.0 (29.6-32.4)	28.5 (26.6-30.5)	26.1 (24.1-28.2)	<.001	AF>HR&LR
STAI-Trait, mean (CI)	40.7 (39.2-42.2)	34.0 (32.1-36.0)	33.5 (31.5-35.7)	<.001	AF>HR&LR
Neuroticism (EPQ)§, mean (CI)	11.8 (10.7-12.8)	8.0 (6.3-9.6)	6.7 (4.5-8.8)	<.001	AF>HR&LR

*=Eleven participants with dyslexia were excluded.

† =Attentional deficit and hyperactivity disorder, eating disorder and adjustment disorder.

‡ =Lamotrigine, Valproate, Lithium.

§=Data were missing for 12 participants from EPQ.

Abbreviations: MZ=Monozygotic, CI=Confidence intervals, NA=Not Applicable, SSRI=Selective Serotonin Reuptake Inhibitor, SNRI=Serotonin-Norepinephrine Reuptake Inhibitor, TCA=Tricyclics Antidepressant, HDRS-17=Hamilton Depression rating Scale, AF=Affected Twins, HR=High-risk twins, LR=Low-risk twins, YMRS=Young Mania Rating Scale, MDI=Major Depression Inventory, STAI=State and Trait Anxiety Inventory, EPQ=Eysenck Personality Questionnaire.

555

556 **Table 1:** Demographic and clinical variables are presented as estimated group means with
557 confidence intervals by the proc mixed procedure in SAS accounting for within twin-pair
558 dependence. All three-way group comparisons of affected (n = 103), high-risk (n = 44) and low-risk
559 twins (n = 36) are reported with p-values whereas significant post-hoc pairwise comparisons are
560 indicated by directions of effects.

Table 2. Non-affective cognitive performance in affected, high-risk and low-risk MZ twins

Affected twins	High-risk twins	Low-risk twins	
(n = 103)	(n = 44)	(n = 36)	
Mean (CI)	Mean (CI)	Mean (CI)	P

TMT-A, sec	27.7 (26.0-29.6)	27.4 (24.8-30.3)	25.7 (21.7-30.3)	.66
TMT-B*, sec	73.3 (67.5-79.5)	73.8 (65.4-83.4)	78.4 (62.2-98.2)	.83
SCIP-D*, total score	72.7 (70.0-75.3)	75.3 (71.3-79.2)	70.4 (62.2-78.6)	.35
VLT-I, no. of words	22.3 (21.5-23.1)	22.9 (21.7-24.1)	20.9 (18.5-23.3)	.25
WMT, no. of letters	18.9 (18.2-19.5)	19.4 (18.5-20.4)	19.7 (18.7-20.8)	.31
VFT, no. of words	13.7 (12.5-14.8)	14.0 (12.3-15.8)	11.6 (8.1-15.1)	.38
VLT-D, no. of words	6.8 (6.3-7.3)	7.3 (6.5-8.2)	5.9 (5.0-7.4)	.15
PST ^a , no. of boxes	10.8 (10.2-11.4)	11.3 (10.4-12.2)	11.7 (10.7-12.7)	.26

*=Data were missing for one participant from the TMT-B, PST (SCIP) and SCIP-D total.

Abbreviations: MZ=Monozygotic, CI=Confidence intervals, TMT-A=Trail Making Task-A, TMT-B=Trail Making Task-B, SCIP-D=Screen for Cognitive Impairment in Psychiatry, Danish, VLT-I=Verbal Learning Test Immediate, WMT=Working Memory Test, VFT=Verbal Fluency Test, VLT-D=Verbal Learning Test Delayed, PST=Processing Speed Test.

Table 2: Variables in non-affective cognition are presented as estimated group means with confidence intervals by the proc mixed procedure in SAS accounting for within twin-pair dependence. Group comparisons of affected (n = 103), high-risk (n = 44) and low-risk twins (n = 36) are reported with p-values.

Table 3. Affective cognitive performance in affected, high-risk and low-risk MZ twins

Affected twins (n = 103)	High-risk twins (n = 44)	Low-risk twins (n = 36)	Group by Group]	[Task
Mean (CI)	Mean (CI)	Mean (CI)	P	df
Attention to and recognition of emotional faces				

Vigilance scores (FDT)*, ms

Masked fear	-3.3 (-21.3-14.6)	-12.5 (-39.4-14.4)	-13.9 (-61.2-33.3)	.80	2, 177
Unmasked fear	15.6 (0-31.2)	-22.2 (-45.9-1.4)	-4.7 (-30.9-21.5)	.03	2, 177
Masked happy	-12.1 (-28.2-4)	-57.4 (-81.9--32.9)	-27.1 (-54.2-0)	.01	2, 177
Unmasked happy	-8 (-27.4-11.5)	-9.9 (-39-19.2)	17.5 (-37.2-72.2)	.60	2, 177

Discrimination accuracy (FERT)*†

Angry	0.44 (0.41-0.46)	0.44 (0.40-0.48)	0.44 (0.40-0.48)	Fear and happy	
Disgusted	0.36 (0.33-0.40)	0.36 (0.31-0.41)	0.38 (0.32-0.44)	.80	2, 181 [2,
Fearful	0.36 (0.33-0.69)	0.37 (0.32-0.41)	0.40 (0.35-0.46)	[.19]	179]
Happy	0.55 (0.53-0.57)	0.57 (0.53-0.61)	0.54 (0.50-0.58)	All six emotions	
Sad	0.42 (0.39-0.44)	0.44 (0.40-0.48)	0.44 (0.39-0.48)	.87	2, 905 [10,
Surprised	0.49 (0.47-0.52)	0.48 (0.44-0.52)	0.44 (0.37-0.52)	[.76]	895]

Response time correct hits (FERT)*, ms

Angry	1484.4 (1382.5-1594.0)	1399.1 (1255.5-1559.2)	1354.6 (1201.7-1527.0)	Fear and happy	
Disgusted	1733.9 (1600.2-1878.8)	1640.8 (1455.3-1850.0)	2091.9 (1642.8-2663.7)	.71	2, 180 [2,
Fearful	1901.9 (1782.9-2028.9)	1923.2 (1748.5-2115.4)	2321.4 (1911.2-2819.6)	[.37]	178]
Happy	1302.6 (1221.4-1389.3)	1233.6 (1120.9-1357.6)	1353.0 (1124.8-1627.6)	All six emotions	
Sad	1597.7 (1485.6-1718.3)	1589.3 (1720.2-1770.6)	1859.1 (1496.7-2309.1)	.74	2, 900 [10,
Surprised	1366.7 (1268.6-1472.3)	1460.6 (1307.9-1631.0)	1693.9 (1353.7-2119.3)	[.63]	890]

Self-referential categorisation and memory

Categorisation accuracy (ECAT)*‡, proportion correct

Positive words	93.7 (92.2-95.0)	94.3 (92.2-96.6)	94.3 (90.2-97.4)	.15	2, 163
Negative words	94.5 (93.3-95.6)	94.7 (92.8-96.2)	95.7 (93.8-97.2)	[.81]	[2, 161]

Response time categorisation (ECAT)*‡, ms

Positive words	1072.7 (1018.5-1124.8)	1066.8 (984.7-1048.2)	957.6 (867.0-1048.2)	.20	2, 163 [2,
Negative words	1147.9 (1089.2-1206.6)	1144.6 (1054.0-1235.3)	1034.2 (934.1-1134.3)	[.99]	161]

Number recalled (EREC)*‡, range 0-45

Positive words	3.3 (2.8-3.8)	3.6 (2.9-4.4)	4.1 (3.3-4.9)	.08	2, 164 [2,
Negative words	2.9 (2.5-3.3)	3.5 (2.9-4.1)	3.6 (2.8-4.3)	[.60]	162]

Emotion reactivity and regulation in social scenarios

Emotion ratings (SST)*‡, range 0-100

Neutral	5.3 (3.2-7.7)	4.6 (2-8.4)	1.9 (0.1-6.4)	Negative react and dampen	
Negative react	74.7 (70.7-78.4)	67.6 (61.2-73.6)	61.5 (48.0-74.1)	.30	2, 169 [2,
Negative dampen	46.4 (42.6-50.3)	46.1 (40.2-52.0)	46.4 (40.0-52.9)	[.26]	167]
Positive react	78.5 (75.2-81.5)	77.6 (72.6-82.2)	73.6 (66.6-84.6)	Positive react and dampen	
Positive dampen	56.6 (52.4-60.8)	61.3 (54.8-67.5)	61.4 (54.5-68.1)	.69	2, 167 [2,
				[.33]	165]

Habitual coping strategies

Self-reported use (CISS)*, range 0-80

Task-oriented	51.8 (49.5-54.1)	57.0 (53.5-60.6)	54.0 (48.5-59.5)	.04	2, 159
Emotion-oriented	42.7 (40.0-45.5)	35.7 (32.3-39.4)	34.8 (31.4-38.5)	<.001	2, 159
Avoidance-oriented	39.5 (37.8-41.2)	37.6 (35.0-40.3)	40.9 (37.8-43.9)	.24	2, 159

*=Data were missing for two affected twins from FDOT, one affected twin from FERT, four affected twins, one high-risk and three low-risk twins from ECAT, three affected, one high-risk and three low-risk twins from EREC, one affected and one low-risk twin from SST, 13 affected and seven high-risk twins from CISS.

†=Scores of discrimination accuracy tend to 1, 0, and -1 reflecting better than chance, close-to-chance and worse-than-chance.

‡=Eleven participants with dyslexia were excluded.

Abbreviations: MZ=Monozygotic, CI= Confidence intervals, FDOT=Faces Dot-Probe Task, FERT=Facial Expression Recognition Task, SST=Social Scenarios Task, CISS=Coping Strategies in Stressful Situations, ECAT= Emotional Categorisation Task, EREC=Emotional Recall

task.

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578 **Table 3:** Variables of affective cognition are presented as estimated group means with confidence
579 intervals by the proc mixed procedure in SAS accounting for within twin-pair dependence. Group
580 comparisons of affected (n = 103), high-risk (n = 44) and low-risk twins (n = 36) are reported with
581 unadjusted p-values and degrees of freedom. Subheadings in the test result column indicate within
582 subjects factors in repeated measurements analysis.

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593 **Figure 1.** High-risk twins showed attentional avoidance of emotional faces.

594 Vigilance scores are calculated as response time difference in ms. identifying probes shown after emotional faces over neutral faces
595 (i.e. positive values represent attention bias towards emotional faces, negative values represent attentional avoidance). Unmasked

596 condition: Face stimuli shown for 100 ms, masked condition: Face stimuli shown for 17 ms. Data are presented as estimated means of
597 vigilance scores from the mixed procedure in SAS. Error bars represent standard error of the mean. * $P < .05$.